Resistant Anemia in CKD Patients

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Agenda

- Overview.
- Definitions.
- Causes of ESA Hyporesponsiveness.
- KDIGO Guideline.
- NICE Guideline.
- New Anemia Therapies.

Overview

- The anemia of CKD is principally due to reduced renal erythropoietin (EPO) production and, to a lesser degree, to shortened red cell survival.
- Anemia can develop well before the onset of uremic symptoms due to ESRD.
- Most of the paients with renal anemia respond well to erythropoietic stimulating agents (ESA).
- Some patients are relatively resistant to ESAs and require large doses. This poor response to ESA therapy may be associated with increased mortality.

Bradbury BD, Danese MD, Gleeson M, Critchlow CW. Effect of Epoetin alfa dose changes on hemoglobin and mortality in hemodialysis patients with hemoglobin levels persistently below 11 g/dL. Clin J Am Soc Nephrol 2009; 4:630.

Overview

- **A large ESA requirement is defined as either :**
  - ✓ the requirement of excessive doses during initiation of therapy, or
  - ✓ inability to achieve or maintain target hemoglobin levels despite the large dose in the iron-replete patient.

Erythropoiesis – stimulating agents

ESA	Approval		Characteristics	Half-life	Frequency administration
	FDA	EMA			
Short-acting					
Epoetin beta		1989	Identical a.a. and carbohydrate composition to EPO	i.v. 4 - 12 h s.c. 12 – 28 h	3 times/week
Epoetin alpha	1989	1989	Identical a.a. and carbohydrate composition to EPO	i.v. ≈ 5h s.c. ≈ 24h	3 times/week
Epoetin zeta (biosimilar medicine)		2007	Identical a.a. and carbohydrate composition to EPO	i.v. ≈ 5h s.c. ≈ 24h	3 times/week
Epoetin theta (biosimilar medicine)		2009	Identical a.a. and carbohydrate composition to EPO	i.v.≈ 4h s.c. ≈ 34h	3 times/week

Erythropoiesis – stimulating agents

Long-acting					
Darbopoetin alpha	2001	2001	2 additional N-linked carbohydrate chains compared to EPO	i.v. 21 hours s.c. 73 hours	once/week
Methoxy polyethylene glycol-epoetin beta	2007	2007	continuous erythropoietin receptor activator	i.v. 134 hours s.c. 139 hours	once/month
Peginesatide	2012		PEGylated, homodimeric peptide with no sequence homology to rhEPO		once/month

FDA – Food and Drug Administration;
EMA – European Medicines Agency

Definitions

- According to the European best practice guidelines (EBPG):

  The resistance to ESAs is defined as a failure to achieve target Hb levels (11– 12 g/dl) with doses lower than 300 IU/kg/ week of epoetin or 1.5 µg/kg/ week of darbopoietin-α.

Locatelli, F, Aljama, P, Barany, P, et al. Revised European best practice guidelines for the management of anaemia in patients with chronic renal failure. Nephrol Dial Transplant (2004). Suppl 2:ii, 1-47.

Definitions

- For NKF KDOQI guidelines,

Hyporesponsiveness to ESAs therapy is defined by, at least, one of these situations:

1. a significant increase in the ESA dose required to maintain a certain Hb level,
2. a significant decrease in Hb level at a constant ESA dose or
3. a failure to increase the Hb level to higher values than 11 g/dL, despite the administration of an ESA dose equivalent to epoetin higher than 500 IU/kg/week.

KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Anemia in Chronic Kidney DiseaseAm J Kidney Dis (2006). S, 11-145.

Definitions

- KDIGO defines :

➢ initial hyporesponsiveness as having no increase in hemoglobin concentration after the first month of appropriate weight-based dosing.

➢ acquired hyporesponsiveness as requiring two increases in ESA doses up to 50 percent beyond the dose at which the patient had originally been stable.

➢ ***KDIGO clinical practice guidelines for anemia in chronic kidney disease. Kidney Int Suppl 2012; 2:288.***

Causes of ESA Hyporesponsiveness

1) Iron deficiency:
2) Bone disease due to secondary hyperparathyroidism;
3) Chronic inflammation
4) Although now rare, the accumulation of aluminum (Aluminum overload). !!!
5) Inadequate dialysis.
6) ACE inhibitors and ARBs. may result in relative ESA resistance.

Causes of ESA Hyporesponsiveness

7) Occult malignancy and unsuspected hematologic disorders (eg; vitamin B12 and folate deficiency, Hemoglobinopathies and Multiple myeloma/ myelofibrosis/ myelodysplastic syndrome).

8) Development of pure red cell aplasia associated with the presence of neutralizing anti-EPO antibodies in patients treated with particular brands of ESA by the subcutaneous route.

9) Presence of human immunodeficiency virus (HIV) infection.

Iron deficiency

- The most common cause, which may be due to external blood losses and/or exhaustion of iron stores due to an increase in erythropoiesis caused by ESA treatment.

- Iron-restricted erythropoiesis is frequent in CKD patients and is due to absolute or functional iron deficiency.

- It is important to distinguish between absolute and functional iron deficiency.

Johnson, D. W, Pollock, C. A, & Macdougall, I. C. Erythropoiesis-stimulating agent hyporesponsiveness. Nephrology (Carlton) (2007). , 12, 321-330.

Iron deficiency

- Indeed, there is a controversy about iron supplementation when TSAT is lower than 20% and ferritin is higher than 500ng/mL (functional deficiency).

- In this situation, probably associated with an inflammatory response, an excess of iron can be potentially harmful to these patients.

Johnson, D. W, Pollock, C. A, & Macdougall, I. C. Erythropoiesis-stimulating agent hyporesponsiveness. Nephrology (Carlton) (2007). , 12, 321-330.

Inflammation

possibly due to enhanced cytokine production.

- This is also consistent with the observation that an increased number of vascular access-related infections and dialysis catheter insertions are associated with higher ESA requirements.
- The anemia of CKD is often referred as an inflammatory anemia.
- Inflammation is a common feature in CKD patients, mainly, in those under HD.

Costa, E, Lima, M, Alves, J. M, et al. Inflammation, T-cell phenotype, and inflammatory cytokines in chronic kidney disease patients under hemodialysis and its relationship to resistance to recombinant human erythropoietin therapy. J Clin Immunol (2008). , 28, 268-275.

Inflammation

- Usually, HD patients present with high levels of inflammatory markers, namely, IL-6, CRP, TNF-α, INF-γ, and with lower serum levels of albumin.
- A weak response to ESA also appears to be associated with enhanced T cell capacity to express IFN-γ, TNF-α, IL-10, and IL-13.

Costa, E, Lima, M, Alves, J. M, et al. Inflammation, T-cell phenotype, and inflammatory cytokines in chronic kidney disease patients under hemodialysis and its relationship to resistance to recombinant human erythropoietin therapy. J Clin Immunol (2008). , 28, 268-275.

Inflammation

Inflammation contributes to anemia through several ways:

- Suppression of erythropoiesis:

✓ **directly**, by the inhibitory effects of pro-inflammatory cytokines: IL-1β and TNF-α

✓ **indirectly** as IL-1β and TNF-α stimulate the production of INF-γ, known to mediate erythropoiesis suppression.

- Accelerated destruction of erythrocytes by the reticulo-endothelial macrophages activated by the inflammatory state.

Original Report: Laboratory Investigation

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Neutrophil Activation and Resistance to Recombinant Human Erythropoietin Therapy in Hemodialysis Patients

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Abstract

Aim: The aim of this work was to evaluate the neutrophil activation state in chronic kidney disease (CKD) patients under hemodialysis, and its linkage with resistance to recombinant human erythropoietin (rhEPO) therapy. ***Methods:*** We studied 63 CKD patients under hemodialysis and rhEPO treatment (32 responders and 31 non-responders to rhEPO therapy). In 20 of the CKD patients (10 responders and 10 non-responders to rhEPO therapy), blood samples were also collected immediately after dialysis. Twenty-six healthy volunteers were included in a control group. Hemoglobin levels, total and differential leukocyte counts, and circulating levels of C-reactive protein (CRP), elastase and lactoferrin were measured in all patients and controls. ***Results:*** Compared with controls, CKD patients presented with significantly higher CRP, neutrophil and elastase levels. When we compared the 2 groups of patients, we found that non-responders presented statistically significantly higher elastase plasma levels. A positive significant correlation was found between elastase levels and weekly rhEPO dose and CRP serum levels. After the hemodialysis procedure, a statistically significant rise in elastase, lactoferrin and, elastase/neutrophil and lactoferrin/neutrophil ratios were found. ***Conclusions:*** Our data show that CKD patients under hemodialysis present higher elastase levels (particularly in non-responding patients), which could be related to the rise in neutrophils, and to be part of the enhanced inflammatory process found in these patients.

Inflammation

Inflammation contributes to anemia through several ways:

- Reduction of EPO production: IL-1β and TNF-α increase the expression NF-κB, inhibitory of the transcriptional factors of EPO gene.

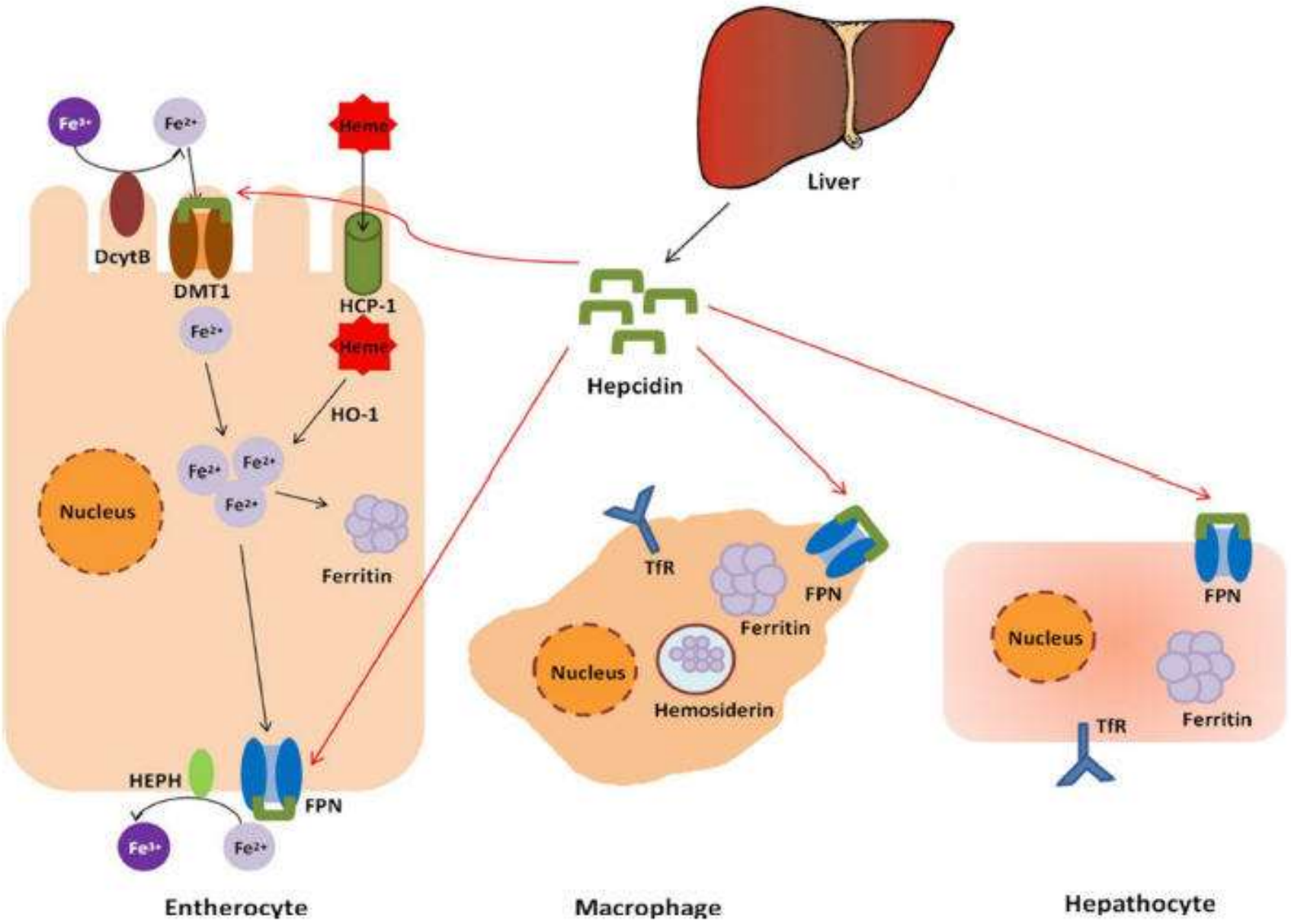
- Impaired iron availability for erythropoiesis: transferrin receptors in erythroid and non erythroid cells can be down-regulated by inflammatory cytokines reducing iron uptake

Decreased hepcidin excretion

- An increase of hepcidin levels leads to a decrease in iron absorption and an inhibition of iron release from its storages (macrophages and hepatocytes),

- As hepcidin binds to ferroportin (the only known iron exporter in the cells) promoting its internalization and degradation in lysosomes.

Mena, N. P, Esparza, A, Tapia, V, Valdes, P, & Nunez, M. T. Hepcidin inhibits apical iron uptake in intestinal cells. Am J Physiol Gastrointest Liver Physiol (2008). G, 192-198.



Iron metabolism and hepcidin

Decreased hepcidin excretion

- Hepcidin is increased in HD patients, and it is regulated by inflammation and linked to ESA resistance.

- Hepcidin correlates with IL-6, the cytokine that stimulate its production, and with ferritin reflecting high inflammation and high levels of iron stores.

- Hepcidin could be a marker of functional iron deficiency and that ESA therapy can decrease hepcidin levels.

Won, H. S, Kim, H. G, Yun, Y. S, et al. IL-6 is an independent risk factor for resistance to erythropoiesis-stimulating agents in hemodialysis patients without iron deficiency. Hemodial Int (2012). , 16, 31-37.

Secondary hyperparathyroidism

- this should be suspected when ESA resistance occurs in iron-replete patients in the setting of severe hyperparathyroidism.
- Several mechanisms have been proposed as

➢ interference with RBC production as PTH causes bone marrow fibrosis,

➢ has an inhibitory effect on BFU-E and interferes with EPO endogenous production ;

➢ interference with RBC survival as PTH increases osmotic fragility of erythrocytes.

Brancaccio, D, Cozzolino, M, & Gallieni, M. Hyperparathyroidism and anemia in uremic subjects: a combined therapeutic approach. J Am Soc Nephrol (2004). Suppl1:S, 21-24

Inadequate dialysis

- Inadequate dialysis is associated with the need for higher ESA doses.
- Some studies showed that convective treatments present benefits in ESA response, as compared with other treatments.
- High flux HD (HF-HD) and online hemodialfiltration (OL-HDF) improve the response to ESAs, as compared to low flux HD (LF-HD), probably due to a better removal of middle and large molecules that impair erythropoiesis.

Johnson, D. W, Pollock, C. A, & Macdougall, I. C. Erythropoiesis-stimulating agent hyporesponsiveness. Nephrology (Carlton) (2007). , 12, 321-330.

In-Depth Review

Blood Purif 2011;32:210–219
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Impact of Hemodialysis Therapy on Anemia of Chronic Kidney Disease: The Potential Mechanisms

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Abstract

A significant and increasing number of chronic kidney disease (CKD) patients are treated with online hemodiafiltration (OL-HDF), even in the absence of more conclusive survival data. OL-HDF affords several clinical benefits including control of anemia of CKD, a common affliction in dialysis patients. In efforts to understand the underlying mechanisms that contribute to the purported benefits of OL-HDF, we examined the potential role and impact of OL-HDF on key stages of anemia and its correction: erythropoiesis of bone marrow, circulating erythrocytes and on anemia therapy. We review evidence that indicates OL-HDF may modulate key processes of anemia and its therapy, including underlying conditions and responses of uremic toxicity and inflammation that aggravate anemia. Our assessment indicates that OL-HDF favorably impacts anemia by not only eliminating putative uremic inhibitors that suppress erythropoiesis, reducing red cell destruction and increasing iron availability, but also by mechanisms restricting underlying inflammation and endothelial dysfunction that are crucial to both CKD and anemia.

ACEI and ARBs

- They can act through several mechanisms, not well understood, including inhibition of angiotensin-induced EPO release and

- increased plasma levels of N-acetyl-serylaspartyl-lysil-proline that impairs the recruitment of pluripotent hemopoietic stem cells.

Priyadarshi, A, & Shapiro, J. I. Erythropoietin resistance in the treatment of the anemia of chronic renal failure. Semin Dial (2006). , 19, 273-278.

KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease

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http://www.kidney-international.org

EVALUATING AND CORRECTING PERSISTENT FAILURE TO REACH OR MAINTAIN INTENDED HEMOGLOBIN CONCENTRATION

Frequency of monitoring

3.12.1: During the initiation phase of ESA therapy, measure Hb concentration at least monthly. (*Not Graded*)

3.12.2: For CKD ND patients, during the maintenance phase of ESA therapy measure Hb concentration at least every 3 months. (*Not Graded*)

3.12.3: For CKD 5D patients, during the maintenance phase of ESA therapy measure Hb concentration at least monthly. (*Not Graded*)

Initial ESA hyporesponsiveness

3.13.1: Classify patients as having ESA hyporesponsiveness if they have no increase in Hb concentration from baseline after the first month of ESA treatment on appropriate weight-based dosing. (*Not Graded*)

3.13.2: In patients with ESA hyporesponsiveness, we suggest avoiding repeated escalations in ESA dose beyond double the initial weight-based dose. (2*D*)

Subsequent ESA hyporesponsiveness

3.14.1: Classify patients as having acquired ESA hyporesponsiveness if after treatment with stable doses of ESA, they require 2 increases in ESA doses up to 50% beyond the dose at which they had been stable in an effort to maintain a stable Hb concentration. (*Not Graded*)

3.14.2: In patients with acquired ESA hyporesponsiveness, we suggest avoiding repeated escalations in ESA dose beyond double the dose at which they had been stable. (2*D*)

Management of poor ESA responsiveness

3.15.1: Evaluate patients with either initial or acquired ESA hyporesponsiveness and treat for specific causes of poor ESA response. (*Not Graded*)

3.15.2: For patients who remain hyporesponsive despite correcting treatable causes, we suggest individualization of therapy, accounting for relative risks and benefits of (*2D*):

- decline in Hb concentration
- continuing ESA, if needed to maintain Hb concentration, with due consideration of the doses required, and
- blood transfusions

ADJUVANT THERAPIES

3.16.1: We recommend not using androgens as an adjuvant to ESA treatment. (*1B*)

3.16.2: We suggest not using adjuvants to ESA treatment including vitamin C, vitamin D, vitamin E, folic acid, L-carnitine, and pentoxifylline. (*2D*)

EVALUATION FOR PURE RED CELL APLASIA (PRCA)

3.17.1: Investigate for possible antibody-mediated PRCA when a patient receiving ESA therapy for more than 8 weeks develops the following (*Not Graded*):

- Sudden rapid decrease in Hb concentration at the rate of 0.5 to 1.0 g/dl (5 to 10 g/l) per week *OR* requirement of transfusions at the rate of approximately 1 to 2 per week, *AND*
- Normal platelet and white cell counts, *AND*
- Absolute reticulocyte count less than 10,000/μl

3.17.2: We recommend that ESA therapy be stopped in patients who develop antibody-mediated PRCA. (*1A*)

3.17.3: We recommend peginesatide be used to treat patients with antibody-mediated PRCA. (*1B*)

NCGC National Clinical Guideline Centre

Anaemia Management in Chronic Kidney Disease

Rapid Update 2011

Commissioned by the National Institute for Health and Clinical Excellence

7.3 Detecting ESA resistance

7.3.5 Recommendations

48. After other causes of anaemia, such as intercurrent illness or chronic blood loss have been excluded, people with anaemia of CKD should be considered resistant to ESAs when:

- an aspirational Hb range is not achieved despite treatment with ≥300 IU/kg/week of subcutaneous epoetin or ≥450 IU/kg/week of intravenous epoetin or 1.5 µg/kg/week of darbepoetin, or
- there is a continued need for the administration of high doses of ESAs to maintain the aspirational Hb range [D(GPP)]

49. In people with CKD, pure red cell aplasia (PRCA) is indicated by a low reticulocyte count, together with anaemia and the presence of neutralising antibodies. The GDG considered that PRCA should be confirmed when anti-erythropoietin antibodies are present and there is a lack of pro-erythroid progenitor cells in the bone marrow. [D]

50. In people with anaemia of CKD, aluminium toxicity should be considered as a potential cause of a reduced response to ESAs after other causes such as intercurrent illness and chronic blood loss have been excluded. [C]

7.4 Managing ESA resistance

7.4.5 Recommendations [2006, Updated 2011]

51. In haemodialysis patients with anaemia of CKD in whom aluminium toxicity is suspected, a desferrioxamine test should be performed and the patient's management reviewed accordingly. [C]

52. Consider specialist referral for ESA-induced PRCA. [2006, amended 2011]

AJKD
Narrative Review

New Anemia Therapies: Translating Novel Strategies From Bench to Bedside

Iain C. Macdougall, BSc, MD, FRCP

Am J Kidney Dis. 59(3):444-451.

- During the last few years, newer strategies for correcting anemia have been investigated:

Agent	Active Compound	Manufacturing Process
Peginesatide (Hematide)	Dimeric pegylated peptide	Synthetic peptide chemistry
HIF stabilizers	Prolyl hydroxylase inhibitor	Chemical synthesis
Hepcidin modulation	Various	Various
GATA-2 inhibitors	Small molecule	Chemical synthesis
EPO gene therapy (EPODURE)	Skin cells (microdermis) transfected with the *EPO* gene	Biopump technology, harvesting skin biopsies and using adenovirus as vector

Abbreviations: EPO, erythropoietin; GATA-2, GATA-binding protein 2; HIF, hypoxia inducible factor.

Am J Kidney Dis. 2012;59(3):444-451

- None of the newer agents has outcomes data showing superiority to existing ESAs, and none has been tested in sufficient numbers of hyporesponsive patients to know whether the outcomes in these patients are different from those with conventional ESAs.

- They therefore will need to be subjected to the same degree of scientific investigation as the existing ESAs.


Thank You !